WRITTEN COMMENT FOR THE RECORD

ELAINE LYON, PhD

MEDICAL DIRECTOR OF MOLECULAR GENETICS

ARUP LABORATORIES

ON

GENETIC TESTING

BEFORE

UNITED STATES SENATE

SPECIAL COMMITTEE ON AGING

GENETIC TESTING ROUNDTABLE

JUNE 12, 2008

American
Clinical Laboratory
Association

Senator Smith, other Members of Congress, staff and guests. I am Dr. Elaine Lyon, Medical Director of Molecular Genetics at ARUP Laboratories. As a medical laboratory geneticist, I would like to set the backdrop for today's discussions on the appropriate regulation, validation and medical necessity of genetic testing.

Knowledge gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of disease and its care. Molecular testing improves patient care today and holds promise to further advance care in the future.

Molecular testing allows us to

- Diagnosis difficult and rare diseases (Rett syndrome)
- Detect people highly susceptible to disease before symptoms appear (cancer, colon, breast, ovarian)
- Target which medication to use and when to use it (Tamoxifen, TPMT)
- Manage and monitor diseases effectively (leukemia)

I would like to present examples of mutations known to cause disease, demonstrating the value of appropriate genetic testing. Contrast these to tests for one or more genetic markers that simply show an "association," often weak, with a disease, and for which there has been so much concerned public debate in recent months. More studies are needed before these are ready for "prime-time".

We perform a common genetic test for cystic fibrosis (CF). Since 1989, when Dr. Francis Collins, director of the Human Genome Project, discovered the gene, over 10,000 scientific publications have described its role in this disease. CF is a classic study, not only of the value of genetic tests, but of how the Clinical Laboratory Improvement Amendments (CLIA) allow for the rapid inclusion of new scientific knowledge. I hope there is time later to discuss this in more detail. Several states have now added CF testing to their newborn screening. Without this testing, the diagnosis may be delayed for years because the symptoms can be so vague. Early diagnosis can help prevent malnutrition and diminish lung damage improving longevity for this devastating disease.

One hereditary form of colon cancer—Lynch Syndrome—can be identified in individuals who have a strong family history. For those at risk because of a mutation, cancer screening at a much younger age than is recommended for the general population can improve survival if the cancer is caught early. It will also reduce the anxiety of family members who learn they do not have the mutation and enable them to follow the screening recommended for the general population.

Time does not permit me to share other common examples of clinically important molecular tests in cancer diagnosis, infectious diseases management like HIV and diseases of the blood. We have provided a longer written comment as an attachment that does provide more examples and information.

It is important to address common misconceptions about genetic testing, particularly with respect to validation and regulation.

Validation for analytical accuracy is required for all laboratory developed tests and must be made available to laboratory inspectors. For our CF test we worked closely with the manufacturer to collect data for FDA review.

For the clinical validation of the CF test, we relied on published scientific literature. A standard that I as a laboratory geneticist adhere to is that there must be at least three scientifically sound peer reviewed studies demonstrating a causal or strong link to disease. In some instances, other means of validation are initiated by the lab, consistent with medical practice guidelines and in collaboration with clinicians.

There is a particular challenge to validate tests for rare disease. The NIH encourages laboratories to develop and validate tests for rare genetic diseases that are unlikely to be developed by manufacturers. Their Collaboration, Education, and Test Translation (CETT) program combines the expertise of clinicians, researchers, clinical laboratorians, genetic counselors and patient advocates. It ensures educational material, appropriate testing protocols and good reporting practices.

Molecular tests are available for over 1,500 diseases and conditions and are performed in over 1,200 clinical laboratories in the U.S. Although the FDA has approved relatively few of these individual tests, by volume the cleared tests represent 60-70% of genetic and molecular tests in common usage. The pie chart below graphically depicts this finding. In addition, it has been estimated that as much as 75% of all genetic testing volume performed in the United States is subject to oversight by the State of New York, which carefully examines the clinical validation of new tests. Furthermore, all genetic tests ordered by health care providers are performed in laboratories regulated under CLIA by the Centers for Medicare and Medicaid Services.

As an industry, we recognize that the existing regulatory paradigms of CMS and FDA need to be updated to keep pace with the rapid advances in genetic testing. Accordingly, our industry association, ACLA, has proposed both strengthening CLIA and CMS oversight, as well as greater interagency coordination between FDA and CMS.

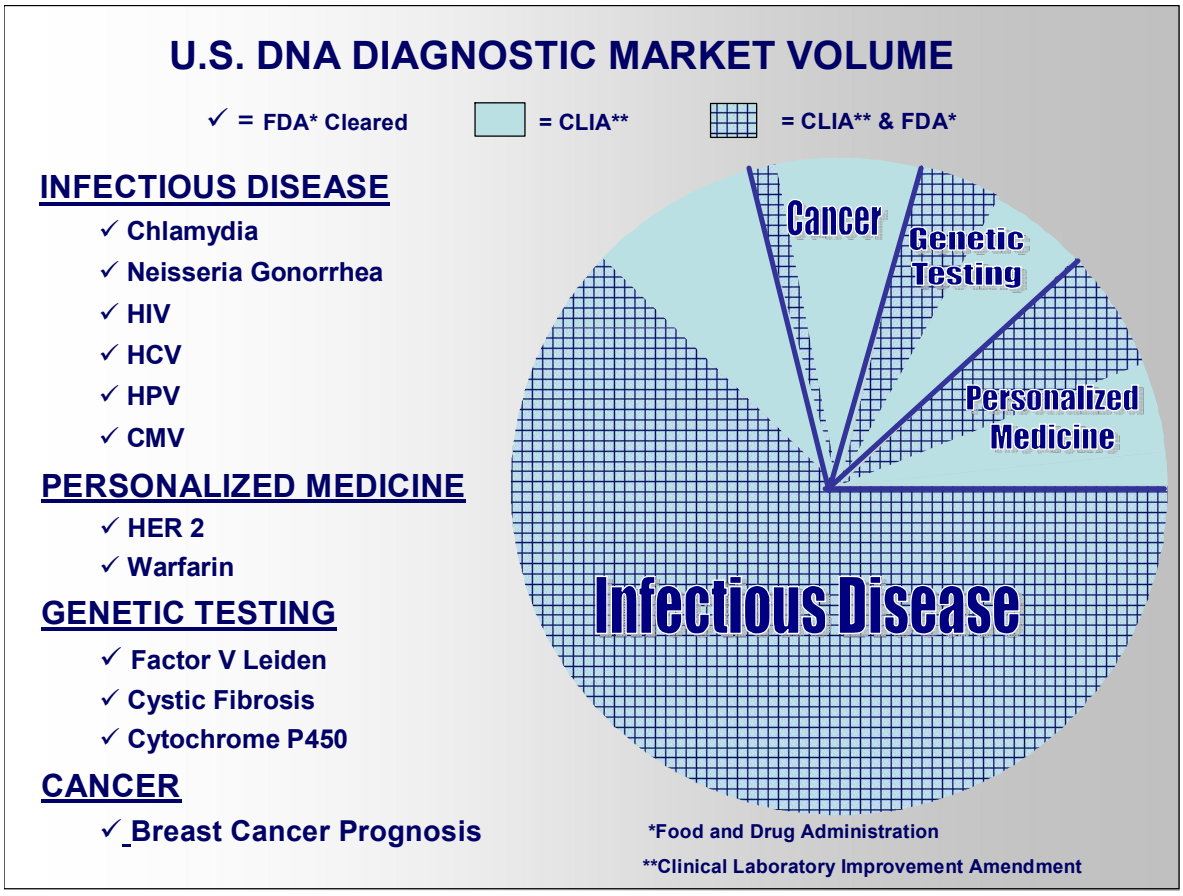
I want to contrast the examples of well established and validated tests with some tests being marketed directly to consumers that make unsubstantiated claims related to disease and provide advice that borders on the practice of medicine. A web based company offers to analyze 5 genes to determine insulin sensitivity. They state that loss of insulin sensitivity may play an important role in common health disorders including type 2 diabetes, high blood pressure, and heart disease. The gene testing result is provided back to the consumer, without any physician examination, glucose testing or HbA1C testing, with suggestions for diet and lifestyle choices – including marketing of vitamins and minerals.

Senator Smith's hearing in 2006 did much to bring attention to certain online companies who market genetic tests directly to consumers and make misleading claims. CMS has properly enforced regulation of those that claimed they need not be CLIA licensed. For those companies that merely market genetic tests performed by other laboratories, any misleading claims about these genetics tests should be investigated by the Federal Trade Commission (FTC). We applaud Senator Smith for raising this issue and support actions to stop these activities.

Let me close with my thoughts for guiding principles to apply to genetic test services:

- Tests should be developed based on sound medical knowledge
- Tests should be ordered by a knowledgeable health care professional who can guide their proper use and interpretation.
- All laboratories which perform these tests should be CLIA certified for high complexity testing
- Exaggerated or unsubstantiated claims should be investigated by the Federal Trade Commission

Innovation in molecular testing is extremely sensitive to regulation and reimbursement. Too much of the former, and too little of the latter, could prevent or delay the hoped-for medical advances. I believe we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise of diagnosing, treating and preventing disease.



American Clinical Laboratory Association

Genetic Test Fact Sheet

Executive Summary

Knowledge gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of disease and its care. It has led to a new era of "personalized medicine" replacing a trail and error approach. Genetic tests are powerful – they allow for the selection of the specific medication that will best treat disease, predict the risk of disease before symptoms occur, and manage the disease more effectively with better information.

Recent media reports could lead one to question the value of genomic based medicine and be concerned that the field is not regulated. That is unfortunate because it sends the wrong message to the public and decision makers. The fact is, the majority of genetic tests by volume are cleared by the Food and Drug Administration or are performed in a laboratory regulated under the Clinical Laboratory Improvement Amendments by the Centers for Medicare and Medicare Services—or both. In addition, clinical laboratories performing genetic tests are regulated by states, and most are additionally overseen by other accrediting bodies.

A concise definition of genetic test remains elusive because genetic tests can refer to analysis performed on human DNA, RNA, genes, and/or chromosomes, human proteins and certain metabolites used to detect inherited or acquired disease and conditions. It is incumbent on all of us to be mindful of this inherent limitation as we discuss important issues such as regulation and validation of genetic tests.

As an industry, we recognize that the existing regulatory paradigms of CMS and FDA need to be updated to keep pace with the rapid advances in genetic testing. Accordingly the American Clinical Laboratory Association has proposed strengthening CLIA and CMS oversight, as well as greater interagency coordination between FDA and CMS.

There are a few bad actors marketing lifestyle, nutritional deficiency, and other tests directly to consumers online with inappropriate and misleading claims. By alleging these tests are for screening and not medical diagnosis, some of these web based companies skirt the CLIA requirements and do not require a physician to order the test and do not provide genetic counseling to help interpret the findings. It is important to distinguish between well established and validated tests with tests being marketed directly to consumers that make unsubstantiated claims to disease and provide advice that borders on the practice of medicine. Companies marketing genetic tests directly to consumers utilizing non CLIA-certified laboratories or making unsubstantiated claims should be investigated by the Federal Trade Commission.

Innovation in molecular testing is extremely sensitive to regulation and reimbursement. Too much of the former, and too little of the latter, could prevent or delay the hoped-for

medical advances. ACLA believes we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise of diagnosing, treating and preventing disease.

I. What is a Genetic Test?

There is no generally accepted definition of "genetic test". A concise definition remains elusive because genetic tests can refer to analysis performed on DNA, RNA, genes, and/or chromosomes, proteins and certain metabolites used to detect inherited or acquired disease and conditions. In some cases there is cross-over between a disease that is inherited and one that is acquired through lifestyle, nutrition and other factors.

This complexity and lack of specificity in the definition can lead to confusion in communication and increases the chance of unintended consequences with regulatory and legislative oversight efforts. It is incumbent on all of us to be mindful of this inherent limitation as we discuss important issues such as regulation and validation of genetic tests.

Setting aside the lack of a precise definition, knowledge gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of disease and in our care for patients. It has led to a new era of "personalized medicine" opportunities that identify genetic differences among individuals and in many cases, customize treatment which holds promise to significantly advance medical care.

One way to look at genetic testing is to consider tests by the laboratory techniques used to examine material taken from blood, urine, cheek or skin cells or tissue samples. These can be considered in three categories:

- Cytogenetics is used to detect chromosomal abnormalities such as the number and shape of chromosomes within a cell by microscope examination, detection of fluorescent probes, or microarray CGH testing (common test is chromosome analysis for trisomy 21(Down syndrome) or fluorescent probes for leukemia's).

- Molecular genetics is used to detect changes at the level of a single or multiple genes or DNA sequence within cells (single inherited gene examples are Cystic Fibrosis or Fragile X syndrome; multiple gene examples are familial colon cancer (Lynch syndrome), an oncology example is bcr/abl monitoring for leukemia, and an infectious disease example is HIV genotyping for drug susceptibility.

- Biochemical Techniques are used to detect markers of changes inhuman proteins and certain metabolites based on genetic function (common examples are phenylketonuria (PKU) the first newborn screening disease and Tay-Sachs disease, an oncology example is HER2 protein detection in tumors).

II. Genetic Tests Have Significant Healthcare Value

These multiple applications of genetic testing allow for the customized treatment or "personalized medicine" approach, which is replacing the trial and error care to diagnosis and treatment. Sales of DNA tests represent about 5% of all diagnostic tests ordered in

the US, and they are the fastest growing segment at about 15% a year. There are many and rapidly growing examples of how genetic tests provide real health care value. Genetic tests are increasingly being used to;

- Select the specific medication that will best treat the disease
- Predict the risk of disease before symptoms occur, allowing earlier treatment or lifestyle changes to avoid disease
- Manage the disease more effectively with better information

Condition	Problem	Personalized Medicine Approach	Result
Selecting the specific medication that will best treat the disease…			
Breast Cancer	Overabundance of HER2 protein on the surface of breast cancer tumors prompts excessive cell growth	Genetic test measures HER2, identifying patients who will benefit from a drug that inhibits its growth	Significant improvement in survival rate. Reduces cancer spread by 50%
HIV	Viral genetic variations make the HIV virus resistant to some anti-retroviral drugs	Tests determine the genetic makeup and rapid mutation of an individual's virus and pinpoint most effective drug	Dramatic improvement in quality, length of life. Patients now can now live for decades
Cardiovascular disease	Genetic variations in the ability to metabolize warfarin, a common blood-thinning drug, often lead to clotting or bleeding	Genetic tests identify the variation	Allows more precise and individualized dosing. Broad use could reduce strokes by 17,000, costs by $1 billion annually
Colon cancer	Due to a gene variation, patients experience life-threatening side-effects from certain colon cancer drugs	Genetic test identifies the variation	Allows physicians to choose other drugs to address cancer
Predicting the risk of disease before symptoms occur, allowing earlier treatment …			
Breast cancer, ovarian cancer	Variations in the BRCA1 and BRCA2 genes increase risks for breast and ovarian cancer	Genetic test identifies the variation	Allows preventive measures, such as closer monitoring and preventive surgery
Colon cancer (Lynch syndrome)	A gene mutation in one of several genes increases the risk for hereditary colon cancer	Genetic tests identify the variation	Allows early and regular screening to enable early detection and treatment
Blood clotting	Individuals with a variation in the Factor V gene and	Genetic test can identify unique variation that increases risk	Allows preventive strategies and medication

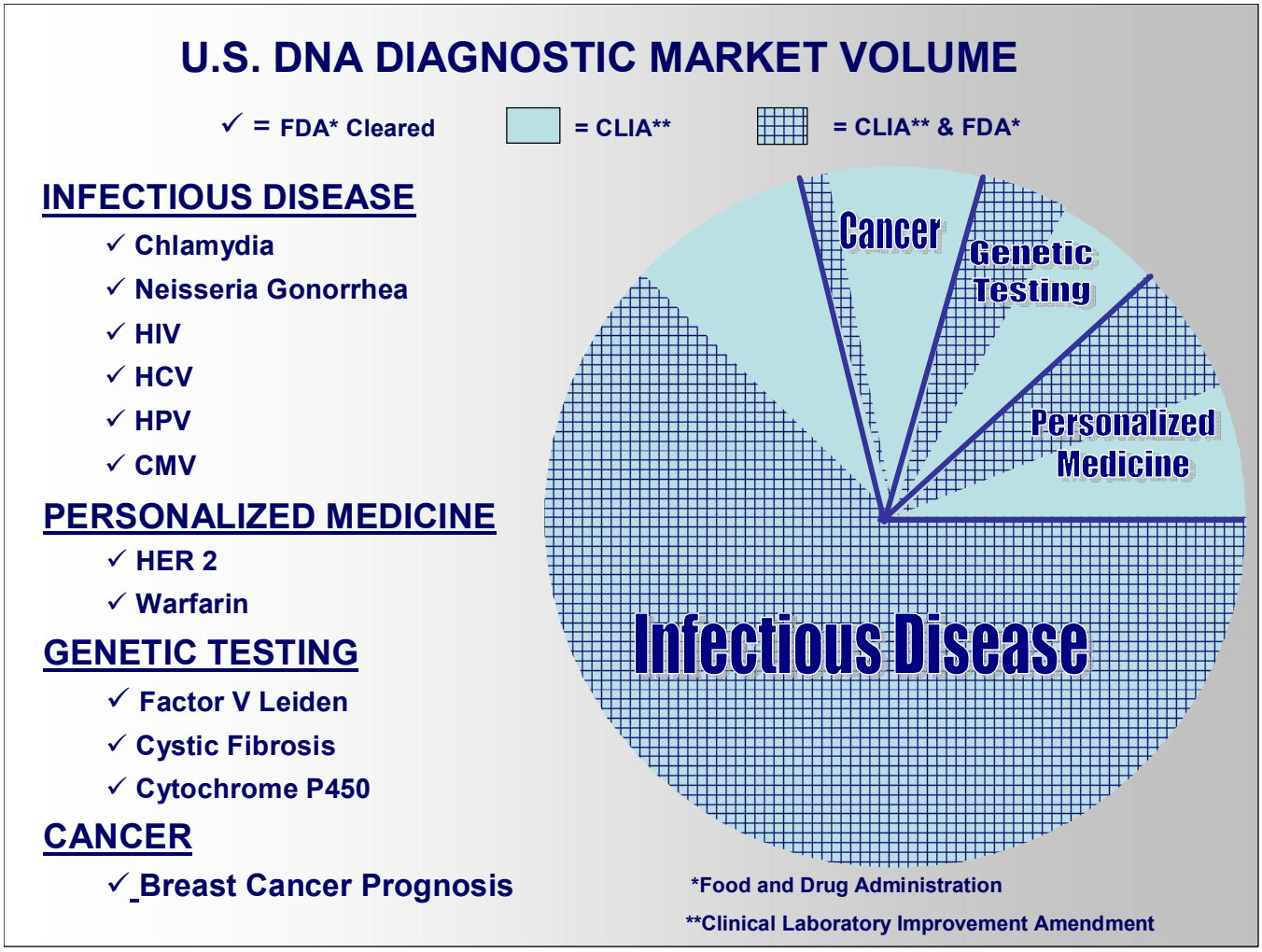
	other genes have five times greater risk of a developing blood clots		to manage clotting
Heart disease	Gene variations increase susceptibility to heart disease and heart attack	Gene tests identify the gene variation	Lets physicians increase the dosage of statin drugs, thus significantly reducing risk of heart attack and coronary heart disease
Melanoma	Gene variation leads to up to 40% of hereditary melanoma cases	Test identifies increased susceptibility to melanoma	Allows preventive steps such as surgery on suspicious lesions, less exposure to sun
Emphysema	Gene variation increases likelihood of liver cancer in patients with emphysema	Genetic test identifies the variation	Allows diagnosis without biopsy; early identification also enables preventive actions
Diagnosing the disease more precisely, leading to more effective treatment…			
Childhood leukemia	Various genetic subtypes of the most common form of childhood leukemia makes "one-size-fits-all" treatment ineffective	Gene tests identify subtypes	Enables physicians to choose drugs and treatment protocols that are geared to the specific genetic subtype. Today's cure-rate for children exceeds 80% vs. 4% in the 1960's
Adult Leukemia	Chromosomal changes create an abnormal protein that increases white blood cells	A genetic test detects the abnormal protein, which can then treated with a genomics-based drug that slows its growth	Better response rates, less toxicity, complete remission in many patients. 5-year survival rate increased from 69% in '01 to 89% today
Cervical Cancer	Certain high-risk strains of the Human Papilloma Virus (HPV), which causes cervical cancer, are difficult to identify	Genetic test identifies the high-risk strains of the HPV	Allows earlier decisions about treatment and frequency of follow-up monitoring
Managing the disease more effectively with better information…			
Breast Cancer	The traditional treatment following surgery for early stage breast cancer is chemotherapy, but it may provide little or no benefit to many women	Gene tests identify an overabundance of specific genes in the tumor itself. This information can be used to quantify the likelihood of cancer recurrence—and the likely need for chemotherapy	Provides more information for physicians and patients to decide whether the benefits of chemotherapy outweigh the side-effects and cost

Cancer	Chemotherapy is often prescribed once cancer has progressed beyond the early, localized stage—yet cancer patients do not respond to chemotherapy 70% of the time	Functional genetic tests can identify with extremely high accuracy those drugs to which the patient's cancer is resistant	Helps in prescribing the most effective treatment, sparing patients unneeded toxicity and saving valuable treatment time
Hereditary hemochromatosis	Hereditary gene variation causes the body to absorb excess iron, leading to liver failure, heart failure, and diabetes	Gene test identifies the variant	Replaces liver biopsy as the first-line confirmatory test for most patients; alerts family members to need for monitoring, preventive therapy
Metabolizing Medications	Gene variations can mean an individual absorbs drugs too slowly or too quickly—leading to "too little" or "too much" of the drug	A molecular test detects the group of enzymes that influence metabolism of about half of all drugs	Allows physicians to make more precise, individualized dosing decisions
Screening to determine if the disease is present…			
Sexually transmitted diseases, hepatitis	Older methods including culturing the bacteria or virus can take days for results	Genetic tests identify these conditions in hours, rather than days	Enables rapid intervention and treatment
Staphylococcus infections	A rapidly-morphing group of bacteria—called Methicillin-Resistant Staphylococcus Aureus—is resistant to drugs	A genetic test can identify this form of Staphylococcus infection rapidly	Helps detect and stop costly, dangerous infections that patients acquire in the hospital

III. Genetic Tests Have Extensive Regulatory Oversight

There are genetic tests for over 1,500 diseases and conditions offered by over 1200 clinical laboratories in the U.S. The Food and Drug Administration has cleared or approved several dozen of these tests, and those approved represent approximately 60-70% of the molecular genetic testing by volume ordered. Genetic tests are performed in laboratories regulated under the Clinical Laboratory Improvement Amendments (CLIA) by the Centers for Medicare and Medicaid Services. In addition, laboratories are regulated by states, and most are additionally overseen by other accrediting bodies.

The pie chart graphically depicts this finding. Furthermore, genetic tests ordered by health care providers are performed in laboratories regulated under CLIA by the Centers for Medicare and Medicaid Services.



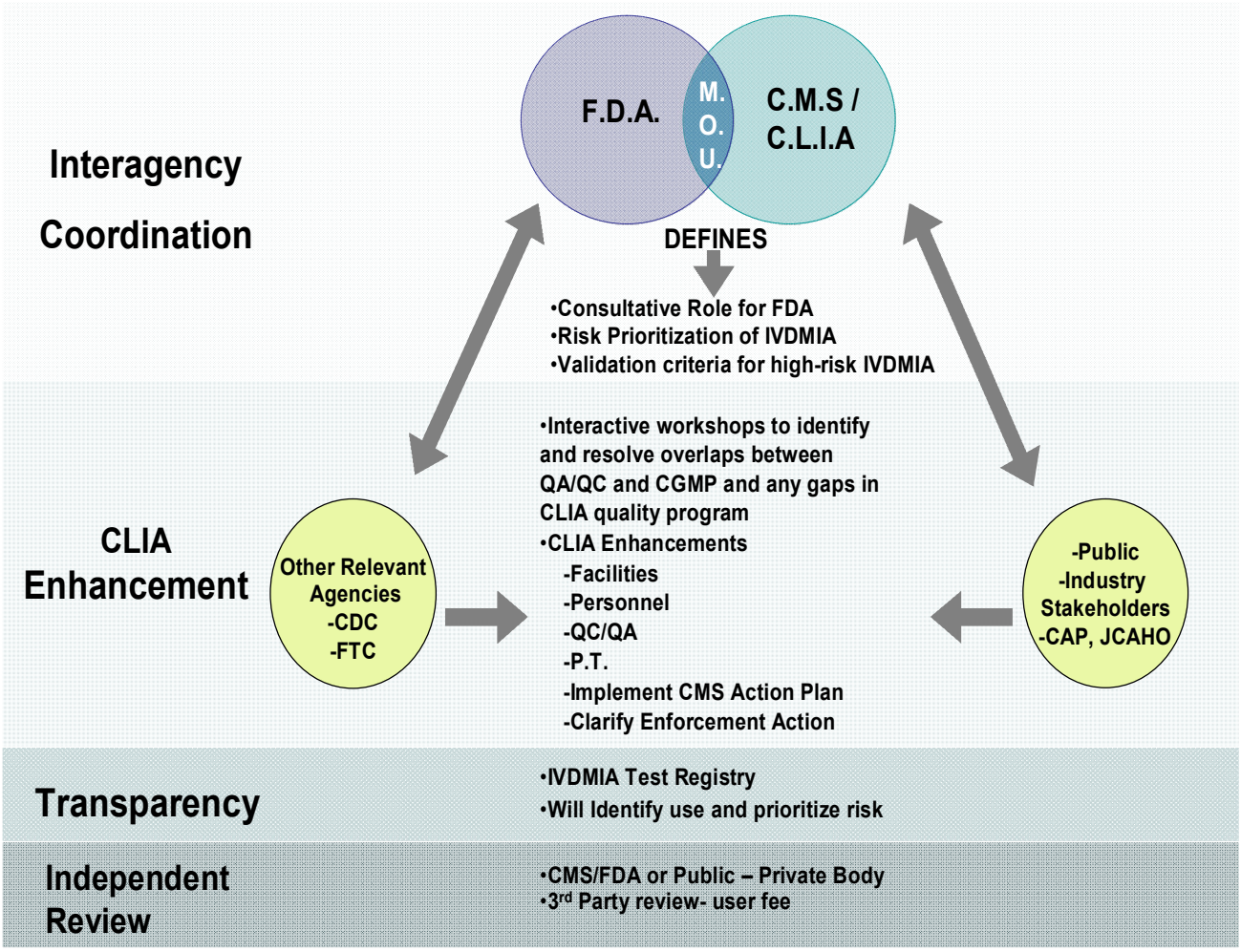
IV. A Proposal to Strengthen CLIA and CMS Oversight

As an industry, we recognize that the existing regulatory paradigms of CMS and FDA need to be updated to keep pace with the rapid advances in genetic testing. Accordingly the American Clinical Laboratory Association has proposed strengthening CLIA and CMS oversight, as well as greater interagency coordination between FDA and CMS. An important aspect of the proposed model is an interagency Memorandum of Understanding (MOU) defining a significant consultative role for the Food and Drug Administration while maintaining the Centers for Medicare and Medicaid Services and CLIA as the exclusive regulatory authority for laboratory test services. The key elements of the proposal are summarized below as bullets; a graphic displaying the key components follows. The key points of the proposal are:

- It is consistent with principles of least burdensome regulation thus avoiding overlapping and potentially conflicting regulatory oversight by maintaining CMS as the sole regulator under CLIA while identifying a significant FDA role.

- It is intended to remedy known concerns by including a mandatory test registry maintained by CMS or by a public-private entity and accessible by the public.
- It can be implemented under law as it exists today through the MOU process and use of interpretive guidelines.
- It is a participatory approach that draws on the expertise of industry stakeholders, CMS, and FDA.
- It does not involve significant new costs for the agencies to build internal expertise or fund a parallel laboratory regulatory oversight structure. User fees would fund third party review of validation packages

Overview of Model



V. What is Needed for the Validation of Genetic Tests

It is important to address common misconceptions about genetic testing, particularly with respect to validation and regulation.

In enacting the Clinical Laboratory Improvement Amendments (CLIA), Congress clearly intended CLIA to be the controlling mechanism for regulating laboratory testing services. CLIA constitutes a comprehensive regulatory scheme that governs nearly every aspect of a laboratory's testing performance. As the agency responsible for CLIA, CMS is responsible for each aspect of validity of laboratory developed genetic tests. The FDA is responsible for ensuring both the analytical validity and clinical validity of commercial genetic test kits manufactured as devices for commercial distribution to third parties, which are not regulated as such under CLIA.

CLIA is fully accepted and recognized as providing a comprehensive, robust approach to all aspects of analytical validity. The requirements and specific approaches to clinical validity should also be an internal function of the laboratory offering the test, if offered as a laboratory developed test. If the laboratory uses an FDA cleared or approved product without modification, it is sufficient for the laboratory director to rely upon the FDA's determination of intended use and clinical significance. If the laboratory offers a test that represents a modification of the FDA cleared or approved product or a laboratory developed test, the laboratory director must ensure that such tests have been appropriately validated. This can be demonstrated by means of peer reviewed papers that report on clinical studies and/or actual clinical studies to the extent that the laboratory performs them to establish clinical validity in different patient subsets.

ACLA supports the principle of data transparency as it relates to making available to clinicians data relevant to the genetic tests they may order, including data regarding the clinical validity of such tests, to the extent that such information is readily available. Data that would be sufficient to demonstrate clinical validity includes that reflected by existing medical guidelines or contained in peer-reviewed literature derived from clinical research. When it is suggested that clinical laboratories should "document current evidence" concerning the clinical validity of tests offered, adequate documentation includes assembling existing medical guidelines or peer reviewed literature derived from clinical studies, but does not necessarily require the clinical laboratory itself to conduct clinical trials. At a minimum the supporting documentation for the clinical validity and utility of a genetic test should include multiple references that provide a reasonable basis for concluding that the test is valid and effective for patient care.

There is a particular challenge to validate tests for rare diseases. The NIH encourages laboratories to develop and validate tests for rare genetic diseases that are unlikely to be developed by manufacturers. Their Collaboration, Education and Test Translation (CETT) program combines the expertise of clinicians, researchers, clinical laboratorians, genetic counselors and patient advocates. It ensures educational material, appropriate testing protocols and good reporting practices.

VI. Problems Raised by Some Direct to Consumer Genetic Tests

There are a few bad actors marketing lifestyle, nutritional deficiency, and other tests directly to consumers online with inappropriate and misleading claims. By alleging these tests are for screening and not medical diagnosis, some of these web based companies

skirt the CLIA requirements and do not require a physician to order the test and do not provide genetic counseling to help interpret the findings. It is important to distinguish between well established and validated tests, on the one hand, and tests being marketed directly to consumers that make unsubstantiated claims to detect disease and provide advice that borders on the unlicensed practice of medicine.

Interest in these direct-to-consumer (DTC) genetic testing companies was enhanced following a hearing by the Senate Special Committee on Aging in 2006. This hearing did much to bring attention to certain online companies who market genetic tests directly to consumers and make misleading claims. CMS has properly stepped up enforcement of those that claimed they need not be CLIA licensed. The Federal Trade Commission (FTC) has released an alert warning consumer's about DTC marketing of genetic tests. Some states have increased the regulation of these tests. But more needs to be done.

ACLA's guiding principles should be applied to all genetic test services:

- Tests should be developed based on sound medical knowledge
- Tests should be ordered by a knowledgeable health care professional who can guide their proper use and interpretation.
- All laboratories which perform these tests should be CLIA certified for high complexity testing
- Exaggerated or unsubstantiated claims should be investigated by the Federal Trade Commission

Innovation in genetic testing is extremely sensitive to regulation and reimbursement. Too much of the former and too little of the latter could prevent or delay the hoped-for medical advances. ACLA believes we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise of diagnosing, treating and preventing disease.

These aberrations should not confuse the public or policymakers. Genetic tests performed in CLIA certified laboratories are safe and are saving and improving lives daily.

For more information on the value of laboratory testing, go to www.labresultsforlife.org or call 202-637-9466.